

CLAIM SUMMARY DOCUMENT

Claim 1 (Previously amended): A method of using a humanized antibody to alpha-4 integrin in the manufacture of a medicament for treating rheumatoid arthritis, wherein the humanized antibody is a humanized form of the mouse 21.6 antibody, wherein said humanized antibody comprises a humanized heavy chain and a humanized light chain:

(1) the humanized light chain comprising three complementarity determining regions (CDR1, CDR2 and CDR3) having amino acid sequences from the corresponding complementarity determining regions of the mouse 21-6 immunoglobulin light chain variable domain designated SEQ ID No:2, and a variable region framework from a human kappa light chain variable region framework sequence except in at least one position selected from a first group consisting of L45, L49, L58 and L69, wherein the amino acid position is occupied by the same amino acid present in the equivalent position of the mouse 21-6 immunoglobulin light chain variable region framework; and

(2) the humanized heavy chain comprising three complementarity determining regions (CDR1, CDR2 and CDR3) having amino acid sequences from the corresponding complementarity determining regions of the mouse 21-6 immunoglobulin heavy chain variable domain designated SEQ ID No:4, and a variable region framework from a human heavy chain variable region framework sequence except in at least one position selected from a second group consisting of H27, H28, H29, H30, H44, H71, wherein the amino acid position is occupied by the same amino acid present in the equivalent position of the mouse 21-6 immunoglobulin heavy chain variable region framework.

Claims 2-17 (Canceled).

Claim 18 (Previously amended): The method according to claim 1, wherein the humanized antibody specifically binds to alpha-4 integrin with a binding affinity having a lower limit of about 10^7 M⁻¹ and an upper limit of about five-times the binding affinity of the mouse 21-6 immunoglobulin.

Claim 19 (Previously amended): The method according to claim 1, wherein the humanized light chain variable region framework is from an RE1 variable region framework sequence except in at least one position selected from the first group, and except in at least one position selected from a third group consisting of positions L104, L105 and L107, wherein the amino acid position is occupied by the same amino acid present in the equivalent position of a kappa light chain from a human immunoglobulin other than RE1.

Claim 20 (Previously amended): The method according to claim 19, wherein the humanized heavy chain variable region framework is from a 21/28'CL variable region framework sequence.

Claim 21 (Previously amended): The method according to claim 20, wherein the humanized light chain variable region framework comprises at least three amino acids from the mouse 21.6 immunoglobulin at positions in the first group and three amino acids from the kappa light chain from the human immunoglobulin other than RE1 at positions in the third group, and the humanized heavy chain variable region framework comprises at least five amino acids from the mouse 21.6 immunoglobulin at positions in the second group.

Claim 22 (Previously amended): The method according to claim 21, wherein the humanized light chain variable region framework is identical to the RE1 light chain variable region framework sequence except for the at least three positions from the first group and the three positions from the third group, and the heavy chain variable region framework is identical to the 21/28'CL heavy chain variable region framework sequence except for the at least five positions from the second group.

Claim 23 (Previously amended): The method according to claim 22, wherein at least three positions from the first group are positions L45, L58 and L69, and the at least five positions from the second group are positions H27, H28, H29, H30 and H71.

Claim 24 (Previously amended): The method according to claim 23, wherein the humanized light chain comprises complementarity determining regions that are identical to the corresponding complementarity determining regions of the mouse 21-6 heavy chain, and the humanized heavy chain comprises complementarity determining regions that are identical to the corresponding complementarity determining regions of the mouse 21-6 heavy chain, except that the CDR3 region of the humanized heavy chain may or may not comprise a phenylalanine residue at position H98.

Claim 25 (Previously amended): The method according to claim 24, wherein the amino acid sequence of the mature light chain variable region is the sequence designated La (SEQ ID NO:7) in Fig. 6 and the amino acid sequence of the mature heavy chain variable region is Ha (SEQ ID NO:11) in Fig. 7.

Claim 26 (Previously amended): The method according to claim 25, wherein the humanized antibody is a Fab fragment.

Claim 27 (Previously added): A method of treating rheumatoid arthritis comprising administering a humanized antibody to alpha-4 integrin, wherein the humanized antibody is a humanized form of the mouse 21.6 antibody, and wherein said humanized antibody comprises a humanized heavy chain and a humanized light chain:

(1) the humanized light chain comprising three complementarity determining regions (CDR1, CDR2 and CDR3) having amino acid sequences from the corresponding complementarity determining regions of the mouse 21-6 immunoglobulin light chain variable domain designated SEQ ID No:2, and a variable region framework from a human kappa light chain variable region framework sequence except in at least one position selected from a first group consisting of L45, L49, L58 and L69, wherein the amino acid position is occupied by the same amino acid present in the equivalent position of the mouse 21-6 immunoglobulin light chain variable region framework; and

(2) the humanized heavy chain comprising three complementarity determining regions (CDR1, CDR2 and CDR3) having amino acid sequences from the corresponding complementarity determining regions of the mouse 21-6 immunoglobulin heavy chain variable domain designated SEQ ID No:4, and a variable region framework from a human heavy chain variable region framework sequence except in at least one position selected from a second group consisting of H27, H28, H29, H30, H44, H71, wherein the amino acid position is occupied by the same amino acid present in the equivalent position of the mouse 21-6 immunoglobulin heavy chain variable region framework.